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Growth and Growth Hormone Secretion After Treatment for Childhood Non-Hodgkin's Lymphoma

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The aim of this study was to evaluate the growth and growth hormone (GH) secretion, as assessed by the rate and pattern of secretion, in patients in remission from non-Hodgkin's lymphoma (NHL) who had been treated with corticosteroids and intense chemotherapy. None of the patients had received cranial irradiation. Twelve children were investigated yearly by taking 24-hour GH profiles starting 1 year from the time of diagnosis. The mean age at onset of the disease was 7.5 years. Another 12 young adults were studied in a cross-sectional manner 4.1–21.3 years (mean, 9.0 years) after diagnosis of NHL. The mean age at onset of the disease was 10.7 years. The median height velocity was significantly decreased during the 1st year following diagnosis (standard deviation scores [SDS] -0.15, $P < .001$), especially during the first 3 months (SDS -0.75, $P < .001$) when the most intense treatment was given. During the 2nd year height velocity was still somewhat reduced (SDS -0.13, $P < .001$). However, there was no reduction in final attained height. Spontaneous GH secretion, in terms of both secretory rate and pulsatile pattern, was evaluated by measuring integrated GH concentrations in 20-minute blood samples collected over a 24-hour period. The plasma GH concentrations were transformed into GH secretion rates by means of a deconvolution technique. Fourier time series analysis was applied to determine possible disturbances of rhythmicity of the GH secretion. The GH secretion rate and the pulsatile pattern of secretion in the NHL patients were similar to those of the reference population of pubertal matched healthy controls. There was no influence of the age at diagnosis or of the time from diagnosis of NHL on the GH secretion rate. Growth impairment in children with a malignant disease treated only with steroids and chemotherapy is therefore probably not caused by disturbed GH secretion, but rather by direct interference with bone growth of the cytotoxic drugs used. There was no significant influence on weight gain during the treatment period so an indirect effect of chemotherapy on bone growth through interference with adequate nutrition seems unlikely. However, GH secretion was not evaluated during the period of growth retardation, and therefore a transient deficiency was not excluded.

Key words: NHL, chemotherapy, growth, growth hormone

INTRODUCTION

Improved survival in malignant disorders in childhood have focused attention on the quality of life of the survivors and especially on the long-term effects of the disease and its treatment. Growth is a sensitive measure of a child's health and has been studied in different childhood malignancies [1]. Growth impairment can be caused by the disease itself, the treatment (chemotherapy, corticosteroids, cranial irradiation), infections, poor nutrition and even psychological factors. It has been shown that growth velocity during treatment is diminished not only in children with brain tumors [2,3] and leukemia [4–6], who receive cranial irradiation as well as cytotoxic drugs, but also in children with non-Hodgkin's lymphoma (NHL) and leukemia who receive steroids and chemotherapy, without irradiation of the central nervous system [7,8].

Children with acute lymphoblastic leukemia (ALL) have been studied during the first 2 years of treatment, including cranial irradiation, and were shown to have normal pulsatile growth hormone (GH) secretion [8]. When studied 4 years or more after diagnosis, however, GH secretion was found to be below that of healthy children of normal height, irrespective of whether the patients had received 18 or 24 Gy to the CNS [9].

While the effect of irradiation on growth has been repeatedly studied, the role of intensive chemotherapy on growth retardation has received less attention. Both a decrease in GH responsiveness in peripheral tissues and a direct interaction of chemotherapy with the secretory function of the pituitary gland could be the operative mechanism. The aim of the present study, therefore, was to investigate whether the spontaneous GH secretion rate and pattern were normal in a group of cured NHL patients

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TABLE I. Patient pubertal stage and time for investigation. Each patient is given a number from 1 to 24. 1–12 = the longitudinal group and 13–24 = the cross-sectional group

Pubertal stage	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	21 Years
Stage 1	2															
	3		3													
	4	4	4		4											
	6	6														
	9	9	9	9												
				10		10										
		11		11												
		12	12	12		12										
Stage 2		2	2													
		5														
Stage 3	7		5				10									
			6	6												
			8													
Stage 4			1	2				10								
				5												
				8												
Stage 5				1	5	16			13	21	22	23		19		18
				7	8					24						
					14											
					17											
				20	20											

Time from diagnosis

who had received steroids and intense chemotherapy but not cranial irradiation.

PATIENTS AND METHODS

Longitudinal Study Group of NHL Patients

Twelve children, (11 boys and one girl), were investigated yearly by taking 24-hour GH profiles starting 1–3 years after the time of diagnosis of NHL. All of them have been investigated at least two times, eight children three times and seven children four times (Table I). Their mean age at the time of diagnosis was 7.5 years (range 1.1–13.4 years) and they were all prepubertal (Table II). Puberty was assessed according to Tanner et al. [10] for pubic hair and breast development. The testicular volume was determined according to the Prader group [11], but was not used for pubertal assessment, because of the known effect of chemotherapy on testicular size.

According to the St. Jude classification for NHL, one patient was stage I, six were stage II, three were stage III, and two were stage IV. Three children were treated with the LSA_2L_2 protocol (Memorial Sloan-Kettering Cancer Center, New York) for 22, 23, and 27 months for T-NHL, respectively, and nine with the BFM 86 protocol (Berlin-Frankfurt-Munster) for B-NHL for a mean of 4 months (range 1–5 months). All children were off treatment at the time for the first investigation. None of the patients received cranial irradiation.

Cross-Sectional Study Group of NHL Patients

The cross-sectional study group consisted of 12 patients, ten men and two women. Their mean age at onset of NHL was 10.7 years (range 0.1–14.7 years), and they were 15.2–27.4 years of age at the time of investigation. They were investigated by taking 24-hour GH profiles at a mean of 9 years (range 4.1–21.3 years) after the diagnosis of NHL. They had all undergone puberty and were at pubertal stage 5 (Table III).

According to the St. Jude staging classification for NHL, three patients were stage I, five were stage II, three were stage III, and one was stage IV. Seven patients were treated with the LSA_2L_2 protocol for 26 months (range 22–36 months), one was treated with the BFM 86 protocol for 3 months, one with the Murphy protocol for 27 months, two with the Swedish protocol for increased risk of leukemia for 30 and 37 months, and one with vincristine and cyclophosphamide for 16 months. None of the patients received cranial irradiation or any other radiation that could affect growth.

Growth Measurements

All of the 24 patients were measured regularly, for standing and sitting height and body weight, from time of diagnosis. Height was measured by experienced staff with a Harpenden stadiometer at diagnosis, every 3 months during the 1st year and thereafter at annual intervals. The values were transformed into standard deviation

TABLE II. Age, height, and pubertal stage in twelve patients treated for NHL: at diagnosis and at time for investigation 1. The longitudinal study group[a]

No	Sex	Disease stage	Treatm prot	Duration of treatment months	At diagnosis			At investigation 1			Midparent height SDS
					Age years	Height SDS	Pub stage	Age years	Height SDS	Pub stage	
1	M	III	A	22	13,4	0,39	1	16,9	0,31	4	0,27
2	M	II	B	4	11,2	1,12	1	12,2	0,76	1	0,44
3	M	IV	B	4	3,3	−0,13	1	4,4	−0,81	1	0,24
4	F	I	B	2	3,0	0,25	1	4,3	1,00	1	−0,38
5	M	II	B	4	12,2	−1,57	1	13,7	−1,38	2	0,02
6	M	II	B	4	7,7	0,42	1	9,0	0,68	1	−0,49
7	M	II	B	5	11,6	2,19	1	12,9	2,06	3	0,27
8	M	III	A	23	11,5	−0,04	1	14,4	−0,31	2	0,52
9	M	III	B	4	6,1	−0,27	1	7,5	0,06	1	0,47
10	M	III	A	27	5,5	1,30	1	9,4	0,54	1	0,80
11	M	II	B	4	1,1	−0,97	1	3,6	−0,56	1	0,43
12	M	IV	B	4	3,5	−0,09	1	5,5	−0,42	1	0,38

[a]A = LSA2-L2; B = BFM 86

TABLE III. Age, height, and pubertal stage in twelve patients treated for NHL: at diagnosis and at time for investigation. The cross-sectional study group.[a]

No	Sex	Disease stage	Treatm prot	Duration of treatment months	At diagnosis			At investigation 1				Midparent height SDS
					Age years	Height SDS	Pub stage	Age years	Time from diagnosis years	Height SDS	Pub stage	
13	M	I	E	37	12,8	1,48	4	21,7	8,9	−0,09	5	*
14	M	IV	A	36	14,2	−1,80	1	22,7	8,5	−1,04	5	0,02
15	M	II	B	3	12,2	−1,57	1	17,2	5,0	−1,02	5	0,02
16	M	III	A	27	12,6	−0,58	1	18,9	6,3	−0,76	5	−0,07
17	M	III	A	23	12,4	0,87	1	17,7	5,3	0,78	5	0,57
18	F	I	D	16	0,1	−1,00	1	21,4	21,3	0,10	5	0,51
19	M	II	A	25	7,3	0,43	1	15,2	7,9	0,91	5	*
20	M	II	A	22	11,5	2,46	2	15,6	4,1	0,06	5	0,27
20	M	II	A	22	11,5	2,46	2	17,1	5,6	−0,40	5	0,27
21	M	II	C	27	9,5	0,73	1	19,8	10,3	0,04	5	0,29
22	M	II	A	26	7,0	0,07	1	18,6	11,6	0,21	5	0,15
23	F	III	E	30	14,2	1,98	1	27,4	13,2	1,67	5	0,79
24	M	I	A	26	14,7	−1,06	1	25,1	10,4	0,60	5	*

[a]A = LSA2-L2; B = BFM 86; C = Murphy; D = Vincristine + cyclophosphamide; E = Swedish protocol for increased risk leukemia. * = missing or not available. Patient number 20 was investigated at two different occasions.

scores (SDS) using Swedish reference values [12]. Final height is defined to be achieved in those children who had gained less than 0.5 cm during the past year and who had reached the age at which they were determined to be at peak height velocity at least 2 years before the last examination [13].

Chemotherapy Schedules

The LSA_2L_2 protocol (Memorial Sloan-Kettering Cancer Center, New York) includes cyclophosphamide, vincristine, prednisolone, methotrexate, daunomycin, cytosine arabinoside, thioguanine, L-asparaginase, lomustine, and hydroxyurea in an induction, consolidation, and maintenance regimen. Five doses of intrathecal methotrexate are given during the introduction and consolidation period, and two doses are given every 10 weeks during maintenance therapy. The BFM 86 protocol (Berlin-Frankfurt-Munster) includes cyclophosphamide, ifosfamide, vincristine, dexamethasone, methotrexate, doxorubicine, cytosine arabinoside, and teniposide (VM-26) in repeated block treatment. Intrathecal combination treatment with methotrexate/cytosine arabinoside/prednisolone is given once or twice per treatment occasion and in doses adjusted to the age of the child. The treatment is given over 5 days at intervals of 2–3 weeks. It is a very intense protocol but of a much shorter duration (6–12 weeks) than the LSA_2L_2 protocol.

Control Subjects

The controls were 117 boys, investigated at the Children's Hospital, Goteborg. Height and weight at the time of the investigation were expressed in standard deviation

scores (SDS), in comparison with the Swedish reference values for healthy children [12]. Both height and height velocity were normal (±2 SD) for all the control children, and they were all healthy, well nourished, and had normal thyroid, liver, and kidney functions. Their chronological ages ranged between 2 and 18 years; 58 were prepubertal, 27 were at pubertal stage 2, 9 were at stage 3, 11 were at stage 4, and 12 were at stage 5 [14].

The study was approved by the Ethical committee of the Medical Faculty, University of Goteborg. Informed consent was obtained from all the children and their parents.

Study Protocol

The children stayed at the hospital for at least a 24-hour period. They received a normal diet, with breakfast at 08.00 hours, lunch at 12.00 hours, and dinner at 17.00 hours and they were allowed normal activity and sleep. A heparinized needle (Carmeda AB, Stockholm, Sweden) was inserted on the first evening or morning. At 08.00–09.00 hours blood collection began using a constant withdrawal pump (Swemed, Goteborg, Sweden) with a nonthrombogenic catheter (Carmeda) as described previously [15]. The rate of withdrawal was 0.5–2 ml/hour, and the volume of the testing system was 0.1–0.2 ml. The heparinized tubes were changed every 20 minutes for 24 h, thus giving 72 samples. The heparinized tubes of blood were stored at room temperature and centrifuged within 24 hours. After centrifugation, the plasma samples were frozen and stored until assayed for GH.

GH Measurement

Concentrations of GH were measured with a commercially available assay (Pharmacia, Uppsala, Sweden) using polyclonal antibodies. In our hands, the intra-assay variation was 10%, 6%, 4%, and 3% at GH concentrations of 2, 5, 15, and 40 mU/L, and the inter-assay variation was 5% at a GH concentration of 10 mU/L and 3% at 40 mU/L. The WHO International Reference Preparation (IRP) of hGH 66/217 was used at the standard [15].

Analysis of 24-Hour GH Profiles

Pulse detection. The GH concentration curves were analysed by the Pulsar program [16] using the previously described setting for GH [15]. This program was the calculated baseline, the number of peaks, peak amplitudes, peak widths, and the area under the curve (AUC). The (AUC) was used to calculate the secreted amount of GH, using a simple formula derived from deconvolution technique [15]. All peaks of GH detected by Pulsar from children belonging to the same sex and pubertal stage were pooled.

Time series analysis. For Fourier time series analysis, the original hormone concentration time series was made stationary by taking the first-order difference [17] and smoothed with a three-point moving average (weights $w_{-1} = w_{+1} = 1/4$, $w_0 = 1/2$) in order to reduce the influence of high-frequency components (low-pass filter). The smoothed series were analysed as Fourier expansions [17], a way of searching for underlying rhythmical components in a sum of sinus and cosinus terms, with periods (frequencies) spanning the whole sampling period (24 hours for a 24-hour profile) down to half the sampling frequency. The resultant amplitude spectral (power) at each frequency is shown in the Results and includes the dominant significant harmonics in the underlying waveform.

Statistics

Significance between means was calculated by one- or two-way analysis of variance followed by Student-Newman-Keul's multiple range test. Changes in height velocity were tested by the Wilcoxon signed rank test.

RESULTS

Height

The changes in SDS for height velocity for all the 24 patients during and after chemotherapy are shown in Figure 1. During the 1st year following diagnosis, the median height velocity was significantly lower than the reference values. The decrease in height velocity was greatest during the first 3 months after diagnosis, when the most intensive treatment was given. The median height velocity SDS was -0.75 ($P < .001$) at 3 months, -0.26 ($P < .001$) at 6 months, and -0.15 ($P < .001$) at 1 year after diagnosis. During the 2nd year median height velocity was still somewhat lowered (-0.13, $P < .001$). There was no difference between the patients who received the BFM protocol and those treated with other protocols. There was no influence on final height for the 12 children in the cross-sectional study group (Table III).

Weight

There was no significant influence on weight gain during the treatment period.

GH Secretion in the Longitudinal and Cross-Sectional Group

The GH secretion rate in U/24 hours in patients who had previously received treatment for NHL was similar to those of the reference group of healthy males at all pubertal stages (Fig. 2). The GH secretion, expressed as the area under the plasma concentration curve above the calculated baseline (AUC_b), as well as the baseline GH levels in the NHL patients were also within the range of the reference subjects (data not illustrated). The GH secretion rate (U/24 hours) at each investigation of the boys of the longitudinal group is depicted in Figure 3.

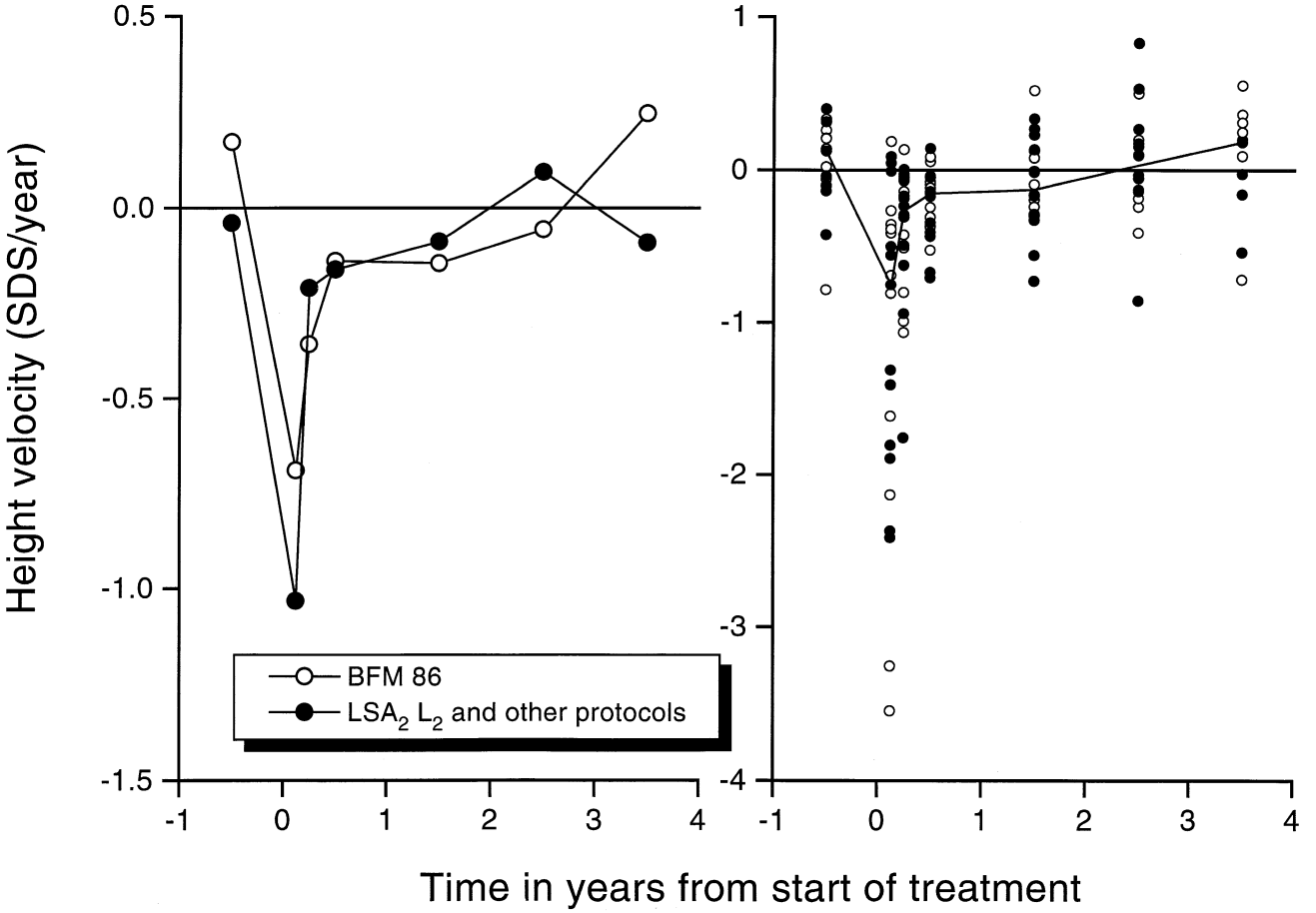

Fig. 1. The median height velocity (SDS) for the two treatment groups (1 = BFM 86 and 2 = LSA_2L_2 and other protocols) (left) and for the combined group (right). The individual height velocity in SDS is also shown (right).

Age at diagnosis of NHL. The NHL patients were aged between 1 month and 14 years at the time of diagnosis. There was no influence of the age at diagnosis on the GH secretion rate in early adulthood.

Time from diagnosis of NHL. The patients in this study were investigated between 4 and 21 years after diagnosis of NHL. No correlation was found between time from diagnosis and the GH secretion rate in early adulthood.

GH Pulsatile Pattern

GH peaks. The maximal GH level during the 24-hour period showed a broad range in the NHL patients, but did not differ from that in normal individuals (Fig. 2). The number of peaks ranged from two to seven in boys and from six to seven in girls, which were within the normal range.

Time sequence analysis. In order to further analyze the possible impact of treatment for NHL on the rhythmicity of the GH profiles we applied Fourier analysis. The periodicity was similar in the NHL patients of all stages of puberty compared to the reference subjects (Fig. 4). The pooled autocorrelation functions from the NHL-treated boys did not differ from that of the control groups (data not illustrated).

DISCUSSION

The main finding from this study of patients with impaired growth during treatment for NHL is that we cannot demonstrate a change in the spontaneous GH secretion, either in terms of secretion rate or in secretory pattern. No influence on GH secretion could be demonstrated either directly after or several years after the treatment period in these patients who had received high doses of cytostatic drugs. Negative findings are, however difficult to interpret, not the least of which is due to the limited number of patients in some of the pubertal stages. Moreover, the intrasubject variability, i.e., reproducibility, known to be around 30%, also has to be considered. [18]

A diminished growth rate in children during treatment for ALL [4,6] and brain tumors [2,3] has been shown

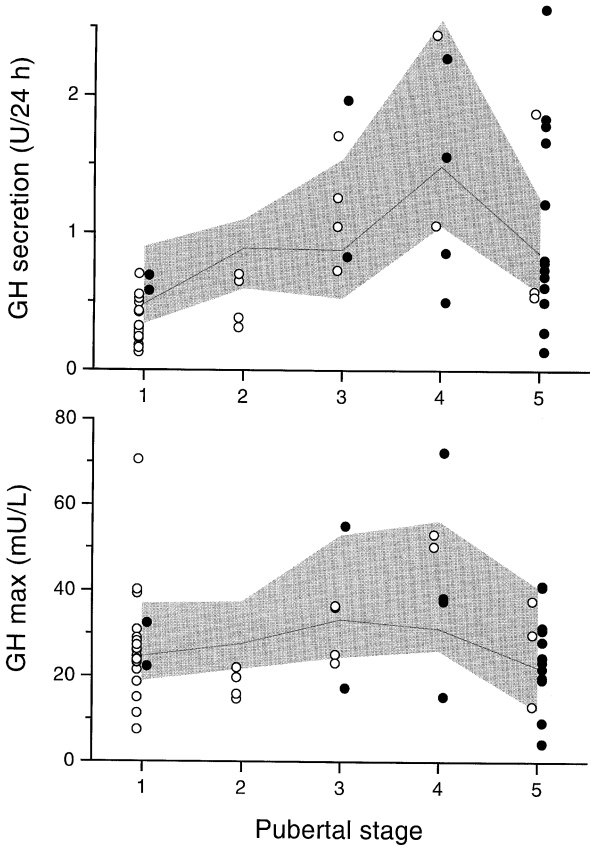

Fig. 2. Individual values of GH secretion rate (upper panel) and the maximal GH level over a 24-hour period (lower panel) are shown for all the investigations of the NHL male patients (both the longitudinal and the cross-sectional groups) treated with BFM 86 protocol (open circles) and LSA_2L_2 and other protocols (solid circles). GH secretion rates of healthy, normally growing boys at pubertal stages 1–5 are also given as the shaded area (75th, 50th, and 25th percentiles).

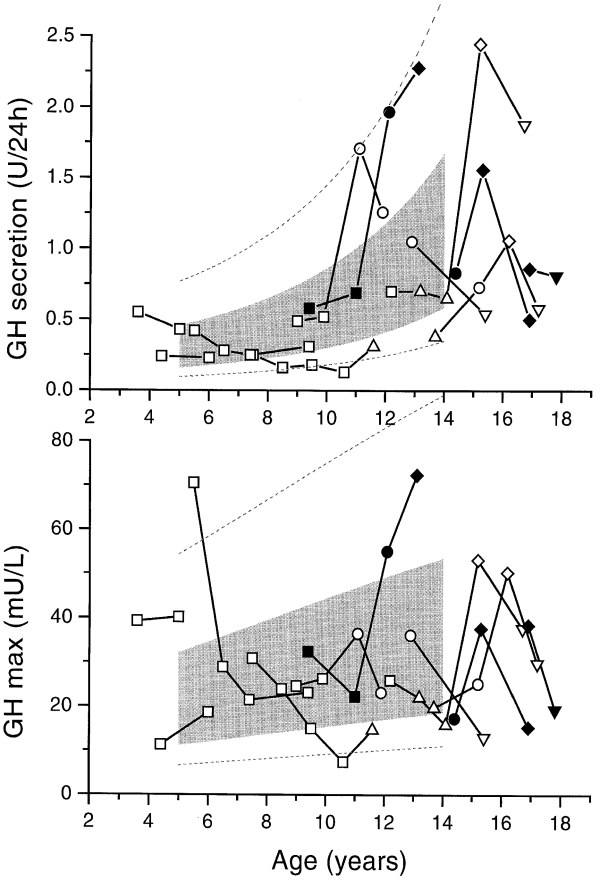

Fig. 3. Individual values of GH secretion rates (upper panel) and the maximal GH levels over a 24-hour period (lower panel) for each investigation of the boys in the longitudinal group. The squares, upright triangles, circles, diamonds, and inverted triangles indicate pubertal stages 1, 2, 3, 4, and 5, respectively. The NHL male patients treated with BFM 86 protocol are shown as open symbols and the LSA_2L_2 and other protocols as solid symbols. The shaded background areas represent ± 1 SD, and the dotted lines represent ± 2 SD of the GH secretion rate and the GH max, respectively, calculated from logarithmically transformed data of the normal prepubertal control boys.

previously. However, it is difficult to discriminate between the adverse effects of cranial irradiation and chemotherapy on growth, and the influence of cytotoxic drugs on growth has receive little attention. There are reports of children with ALL who have been treated with chemotherapy alone and have grown normally [19–23]. Other investigations by Clayton et al. [24] indicate that chemotherapy itself has an effect on growth. In their study, there was catch-up growth in the 3rd year after diagnosis and after 2 years of chemotherapy, irrespective of the radiation schedule. When chemotherapy was given for a further year catch-up growth was delayed by 1 year. Compared with this study Kirk et al. [25] found a greater negative influence on growth in children treated for ALL with chemotherapy and cranial irradiation. Six years after diagnosis, more than two-thirds of the 60 survivors showed a decrease in standing height of more than 1 SD of the population mean. Furthermore, there was a high proportion of patients with GH deficiency assessed both in terms of provocation tests and pulsatile secretion. Kirk et al. [25] considered cranial irradiation to be the main cause of GH deficiency. Their results, however, differed from those of Clayton et al. [24] who found less influence on growth despite a similar radiation schedule to that of Kirk et al. The chemotherapy protocol in the study by Kirk et al. was much more intense, however, both in content and duration, and Clayton et al. hypothesised that this was the major reason for the dissimilar growth patterns seen in the two studies.

Marky et al. [8] investigated GH secretion in children during treatment for ALL and found no difference between children who had received CNS-directed therapy and those who had not. No influence on GH secretion during the 2 treatment years was found, except during corticosteroid treatment periods, when there was a complete, but reversible, suppression of GH secretion. Dacou-Voutetakis et al. [26] studied spontaneous GH secretion in leukemic children before and immediately after cranial irradiation and found that the plasma GH values during

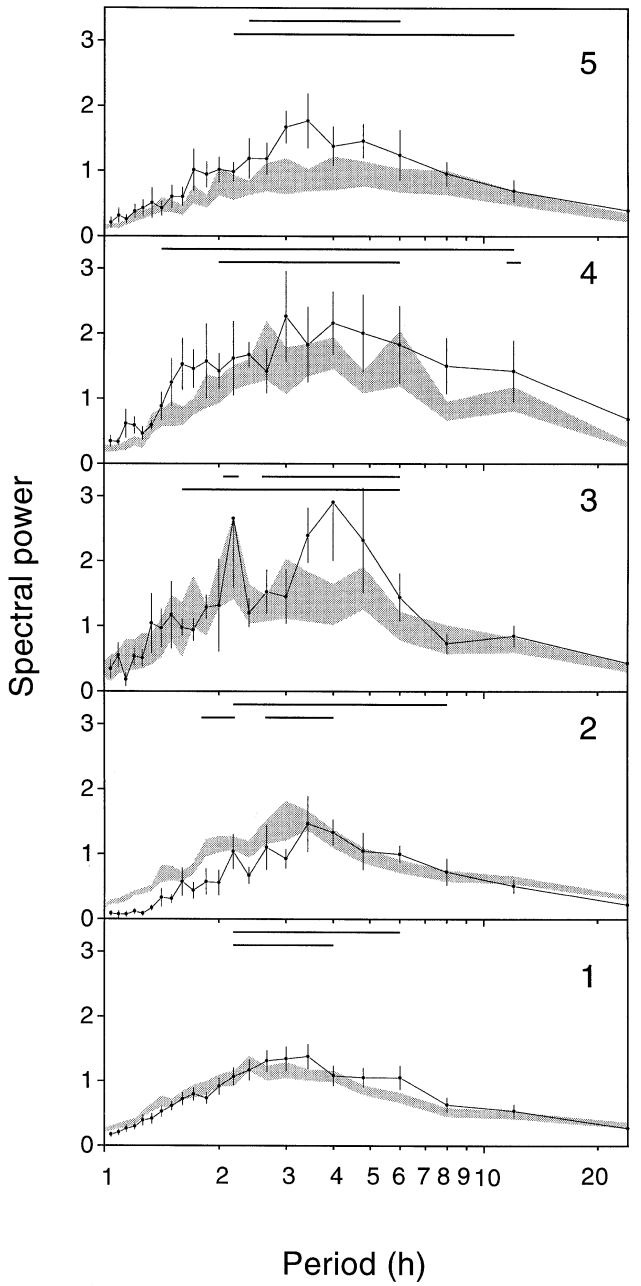

Fig. 4. Fourier analysis of 24-hour GH profiles in NHL boys treated with cytostatic drugs (mean ± SE, vertical bars), compared with the control group of healthy boys (shaded area: ±1 SE) at indicated pubertal stages. The spectral power is shown as a function of the time period. The horizontal lines indicate the broadest nonsignificant range around the peak (dominating period), as analyzed by randomized block analysis of variance, followed by Student-Newman-Keul's multiple range test at the 5% level. The upper horizontal lines at each pubertal stage indicate the NHL boys, and the lower horizontal lines indicate the normal boys. The dominating period of treated NHL boys did not differ from that of the control groups.

chemotherapy, but before radiotherapy, were similar to those in normal children. However, in contrast to the findings of our group, they found a transient decrease in GH secretion after CNS irradiation. After irradiation, a disturbed periodicity with increased number of high-frequency pulses of GH have been found during puberty in a study by Crowne et al., and at 2.5 years median time after cranial irradiation [27], which was not confirmed in a previous study of our group [9]. The difference in results might be due to different treatment schedules, and particularly that of cytostatic drugs. In that respect it was of interest to notice that there was no effect of GH pulsatility in the non-irradiated group given cytotoxic drugs in the present study.

In a previous study [7] we compared the pattern of growth in children with NHL and ALL. The rationale for the comparison was the similarity of the two diseases and their treatment. However, the treatment of NHL and ALL differed in two respects: For NHL, cranial irradiation was not given, while the maintenance treatment was much more intensive than that given for ALL. The influence of the two treatment components on growth could be compared. In both groups of patients, there was growth retardation, which was most pronounced during the 1st year of treatment. Catch-up of growth after the first 2 years of treatment was less in the NHL group than in the ALL group. The children with NHL also showed less catch-up growth after the cessation of therapy. These results were interpreted as an effect of the more intensive chemotherapy given. Sklar et al. [28] analyzed growth and final heights in patients treated for ALL in childhood. Although patients treated with combination chemotherapy and cranial irradiation had the greatest loss in height SDS, significant growth retardation was also found in those treated with chemotherapy alone. In our study all 12 children of the cross-sectional group reached final height. In contrast to Sklar et al. we could not find any negative influence on final height in these children, treated with similar heavy chemotherapy protocols (LSA_2L_2 or high-risk leukemia protocol). Chemotherapy may interfere with the normal growth of the bone itself. Experimental studies indicate that cytotoxic chemotherapy may have a profound effect on the cartilage growth plate [29]. Davies et al. [30] examined the effect of combination chemotherapy and cranial irradiation on final height and body proportions in children treated for ALL. Besides a significant loss of standing height they observed a significant disproportion with a relatively short spine. One of the explanations offered is that chemotherapy could have a direct effect on the epiphysial growth plate, and since the spine contains large numbers of epiphyses, there will be a greater loss in sitting height than leg length. The present study supports the hypothesis that also in the human, chemotherapy influences height velocity, at least transient in the short-term perspective, following initiation of therapy. We can, however, not observe any influence on final height.

From the results of this study. we conclude that the doses of chemotherapy given did not have an effect on the hypo-

thalamic-pituitary axis with reduced secretion of GH, since neither the amount nor the pattern of GH secretion was disturbed. While this investigation showed no indication of a persistance of GH deficiency, the occurrence of a transient deficiency during chemotherapy (the period of transient growth retardation) has not been excluded.

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